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New Therapeutics in Hypertension

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1. Introduction

Cardiovascular diseases are the leading cause of morbility and mortality worldwide. The main risk factor that contributes to the development of these cardiovascular diseases is hypertension. Hypertension increases the risk of injury in the vascular beds of various target organs such as retina, brain, heart and kidneys. Morbility and mortality associated with hypertension is associated mainly with cardiovascular complications. The main goal in the treatment of hypertension is not only controlling blood pressure (BP), but also reducing cardiovascular risk. (Chobanian et al., 2003)

The therapeutical management of hypertension has advanced considerably in recent decades, both in terms of its efficacy in available treatments as in its safety and tolerability profiles.(Table.1) Multiple effective antihypertensive drugs exist to carry out a logical choice. It is necessary to take into account the pathogenic alterations of renin secretion, sympathetic tone, renal sodium excretion, changes in cardiac output, peripheral vascular resistance and blood volume, without forgetting the individual considerations in each patient. However, none of the antihypertensive drugs currently available are able to control all cases of hypertension by themselves. For this reason, monotherapy alone is not usually able to lower BP to optimal levels in most patients. The use of combination therapy with antihypertensive drugs has become the norm. (Calhoun et al., 2008). However, the number of people with uncontrolled hypertension has increased, despite the innumerable evidence of the benefit of BP control and the advances in therapy. (Kearney et al., 2005)

At present the new knowledge obtained about the renin angiotensin aldosterone system (RAAS), the role of the endothelium and nitric oxide (NO), and the ion channels in the homeostasis of BP among others, have opened new lines of study. Therapeutical developments have recently emerged that could improve control of BP, either because they are new and alternative therapeutic strategies, such as carotid sinus stimulation devices, renal denervation and vaccination or due to the improved knowledge of existing alternatives.

This review will focus on little used antihypertensive drugs or on the emerging and application of new therapeutic strategies such as vaccination, renal denervation and the activation of baroreceptors.

2. Renin inhibitors

The importance of the RAAS in the pathogenesis of cardiovascular and renal diseases and hypertension among them has encouraged research to achieve blocking it partially or

completely. The RAAS is composed of peptides and enzymes that lead to the synthesis of angiotensin (Ang) II, which effects are mediated by the action of AT1 and AT2 receptors and are involved in controlling cardiovascular function and hemodynamic equilibrium. (Morales Olivas & Estañ Yago, 2010)

After more than a century of research on the RAAS, Ondetti and colleagues, discovered in 1977 captopril (first inhibitor of angiotensin converting enzyme or ACE inhibitors). (Ondetti, Rubin & Cushman., 1977) In 1988, Timmermans and colleagues, (Timmermans et al., 1991) developed losartan (first AT1 antagonist receptor or ARBs). Both ACE inhibitors and ARBs have demonstrated their effectiveness in the control of hypertension delay, the natural progression of heart failure (HF), diabetes mellitus, and reverse target organ damage such as cardiac hypertrophy and thereby reduce cardiovascular and renal morbility and mortality. (Chobanian et al., 2003) It is not until 2007 that the Food and Drug Administration (FDA) approved the clinical use of aliskiren (first direct renin inhibitor taken orally). (Nussberger et al., 2002) This new group of drugs may represent a superior therapeutical strategy than that of other drugs that inhibit the RAAS, as they not only inhibit the actions mediated by Ang II synthesis but also the direct actions of prorenin and renin through the stimulation of prorenin receptors.

Decade	Antihypertensive drugs
1950	Reserpine, hydralazine, guanethidine, thiazide diuretics, ganglionic blockers
1960	Spironolactone, α 2 adrenergic receptor agonists, β blockers
1970	α 1 adrenergic receptor antagonists, ECA inhibitors, serotonin antagonists & agonists
1980	Calcium antagonists, imidazoline agonists, potassium channells openers
1990	ARBs, antagonist of endothelin receptors, aminopeptidase A inhibitors, crosslink breakers of the end products of advanced glycation, Rho kinase inhibitors
2000	Ouabain antagonists, urotensin II antagonists, vascular NAD(P)H oxidase inhibitors, modulators of the endocannabinoid, vasopeptidase inhibitors, renin inhibitors, vaccines, renal sympathetic denervation, Rheos system
2010	Dual inhibitors of neutral endopeptidase and angiotensin II blockers Dual inhibitors of endothelin converting enzyme and neutral endopeptidase NO releasing drugs with dual action: NO releasing sartans + NO releasing statins Dual antagonist of angiotensin II and endothelin A receptors

Table 1. Hystoric evolution in antihypertensive therapeutics.

Aliskiren is a potent non peptide renin inhibitor. When there is binding of aliskiren to the active site of renin (S1/S3), it blocks the activity of Asp32 and Asp215 of aspartate residue, thus preventing the conversion of angiotensinogen to Ang I. Aliskiren is a hydrophilic molecule with a high solubility in water, which facilitates their oral bioavailability. Aliskiren is absorbed via the gut, it has a bioavailability of 2.5 to 3%, but its high affinity for renin compensates the low bioavailability of the drug. Following oral administration, the peak concentration is reached within 3 to 4 hours. Its half life is 36 hours reaching its stable level in 7 days. Recent studies suggest that CYP3A4 is the enzyme responsible for aliskiren metabolism. 90% of aliskiren is purified through the feces. (Wood et al., 2003) In controlled clinical trials, aliskiren was shown to be as effective an antihypertensive drug as

monotherapy or ACE inhibitors and ARBs. (Weir et al., 2007) Aliskiren is effective and safe in its combination with thiazide diuretics, ACE inhibitors, ARBs and blockers channels of calcium (Sica et al., 2006, Drummond et al., 2007, Andersen et al., 2008, Parving et al., 2008)

With respect to the incidence of adverse events, serious and non serious, there are no statistically significant differences between placebo and therapeutic doses of aliskiren, only at doses of 600 mg of the drug showed an increase in the number of patients who had diarrhea.

A comprehensive program of clinical trials: the ASPIRE HIGHER was assigned to evaluate the influence of aliskiren on cardiovascular and renal protection beyond their antihypertensive action. This big test covers four broad areas: the cardiorenal morbility and mortality, the cardioprotective, the renoprotective and hypertension with approximately 35,000 patients in 14 studies. (ASPIRE HIGHER Clinical Trial Program) the final results of three are already known.

In the study AVOID (Aliskiren in Evaluation of Proteinuria in Diabetes) aliskiren (150-300 mg/day) was administered to diabetic hypertensive patients with proteinuria. The study found that in 6 months of treatment, the addition of aliskiren to conventional therapy in patients with losartan 100 mg per day, conditioned a further reduction of 20% in the rate of urinary albumin excretion, with a reduction greater than or equal to 50% in the urinary excretion rate of albumin in 24.7% of patients receiving aliskiren compared with 12.5% of patients receiving losartan alone. An important aspect that is worth noting is that the rate of adverse effects did not increase in percentage or statistically with the addition of aliskiren to losartan therapy. (Parving et al., 2008)

The ALOFT study (Aliskiren Observation Of Heart Failure Treatment) evaluated the effect of adding aliskiren to the standard therapy for HF in a group of patients (including an ACE inhibitor or an ARBs, but not both, as well as betablockers and diuretics if needed). The addition of 150 mg of aliskiren conditioned significant reductions in natriuretic peptide (NP), proBNP, and echocardiographic parameters related to diastolic function of patients tested, compared with the group of patients who received conventional treatment. (McMurray et al., 2008)

In the study ALLAY (Aliskiren in Left Ventricular Assessment of Hypertrophy) a group of patients with hypertension, obesity and left ventricular hypertrophy were randomized to receive: aliskiren (300 mg), losartan (100 mg), or the combination of aliskiren and losartan with the doses mentioned. The primary endpoint was the evaluation of decreased left ventricular mass after 34 weeks of treatment in the groups already defined. Aliskiren provided a 15% decrease in left ventricular mass greater than the losartan, and the association of aliskiren and losartan provided a drop of 36% higher than losartan alone. This study confirmed the good tolerability of aliskiren and its combination with losartan. (Solomon et al., 2008)

Although the rest of the clinical trials that make up the ASPIRE HIGHER are not avaible, the use of aliskiren opens a new expectation, not only in the treatment and control of hypertension, but also due to its effects on target organ damage and the reduction of cardiovascular risk.

3. Imidazoline agonists

Many of the antihypertensive drugs that exert their action at the nervous system as methyldopa, clonidine, guanfacine and guanabenz, act by stimulating alpha 2 central receptors located in the pontomedular region and its effect consists in the reduction of the sympathetic outflow with a decrease in the peripheral sympathetic activity, but unfortunately they produce adverse reactions which include sedation, dry mouth and impotence, which high occurrence has determined a progressive decrease in their use.

In 1984, articles on imidazoline receptors located in the central nervous system are beginning to be published, and more recently, drugs capable of acting at this level leading to a peripheral sympathetic inhibition. This mechanism of action similar to the classic agonists differs mainly by a lower incidence of adverse reactions. (Yu & Frishman., 1996)

The existence of imidazoline receptors different from the alpha 2 was established in studies in the brains of cattle which tested the affinity of clonidine with these sites. However, because this drug shares its affinity for both imidazoline receptor as the alpha 2 receptor, new compounds were developed with high selectivity for imidazoline receptors, among which moxonidine and rilmenidine are of the most extensive development. Its action is performed on type I receptors, which include those that exert regulatory actions on BP. (Van Zwieten., 1996) There are also type II imidazoline receptors which are related to the stimulation of insulin release and some metabolic processes in the brain, but not involved in the regulation of BP. Type I receptors when stimulated with direct agonists such as moxonidine and rilmenidine, mediate a fall in BP and heart rate by peripheral sympathetic inhibition. The neural pathway involved has been suggested very similar to that dependent on alpha 2 adrenergic activation. (Chan & Head., 1996) In the case of moxonidine and rilmenidine, its action on type I receptors is predominantly exerted with minimal affinity for alpha 2 receptors.

The central action of the agonist of type I receptors has been demonstrated by studies in which stereotaxic injections have been used in parts of the central nervous system where vasomotor centers are located. The involvement of imidazoline receptors in the antihypertensive action of these compounds has been demonstrated with different techniques including antagonizing its effect through selective antagonists of these receptors. The antihypertensive activity occurs at the expense of reduced central sympathetic activity that leads to a reduction in peripheral vascular resistance and vasodilation. Stimulation of type I receptors by these agonists does not produce significant changes in cardiac output and heart rate, although suppression of episodes of tachycardia and antiarrhythmic activity has been reported. A reduction in plasma levels of catecholamines has also been shown. (Mitrovic et al., 1991)

In animal experimental models a reduction in the left ventricular hypertrophy has been shown, possibly due to sympathetic inhibition. Stimulation of type I receptors located in the kidney is involved to explain the natriuretic effect of these compounds. (Mitrovic et al., 1991) Oral administration of moxonidine determined maximum concentrations after 30 to 60 minutes. The absorption is higher than 90% and no first pass metabolism occurs in the liver. About half of the dose is eliminated without changes in the urine. Plasmatic half-life lasts about two hours but the antihypertensive action is much longer indicating an effect dependent on its accumulation in the central nervous system.

However, repeated doses are not accompanied by plasma accumulation. A glomerular filtration rate <30 ml/min should be considered a contraindication for use. The antihypertensive efficacy of moxonidine has been shown in controlled trials in which its effect has been compared with other classes of antihypertensive drugs that have included atenolol, hydrochlorothiazide, captopril and nifedipine. In all cases the effectiveness of BP control was statistically comparable. The antihypertensive effect is due to a vasodilator effect with reduced peripheral resistance without changes in heart rate and cardiac output. The administration of moxonidine produced a significant reduction in plasma catecholamine levels and long-term use determines reducing left ventricular hypertrophy without changing serum glucose and lipids levels.

The main advantage of moxonidine in relation to classical central agonists is given by a lower incidence of adverse reactions, even though there have been no studies comparing the two classes of drugs. Neither prospective studies have been conducted to demonstrate their protective effect on stroke, myocardial infarction, HF and kidney failure. The pharmacological characteristics of rilmenidine are very similar to those of moxonidine. Thus, experiments were made with a high number of patients in which its vasodilator effect as a result of reduced plasma concentrations of norepinephrine has been demonstrated. Another effect is the reduction of sympathetic baroreflex responses of heart and kidney, while vagal dependent cardiac baroreflex sensitivity is increased. As with moxonidine, left ventricular hypertrophy has proven reduction and be neutral on lipids and glucose levels. (Pillion et al., 1994)

4. Vasopeptidase inhibitors

In the early twenty first century vasopeptidase inhibitors were discovered as a new class of drugs for cardiovascular diseases by simultaneously inhibiting the angiotensin converting enzyme (ACE), thereby inhibiting the production of Ang such as Ang II, Ang 1-7 and Ang 2-8, completely blocking the substrates for the activation of AT1 and AT2 receptors and neutral endopeptidase (NEP), NEP metabolizes NP into inactived molecules, blocking this enzyme determines the increased blood concentrations of NP, such as brain NP, C and D, which decreases peripheral resistance and preload. It increases venous capacitance and promotes natriuretic action. There is a reduction in sympathetic tone, inhibition of catecholamine release and activation of vagal afferent endings, suppressing the tachycardia reflex and vasoconstriction, also promoting structural changes in the myocardial remodelling with a potent hypotensive effect. (Corti et al., 2001)

These drugs inhibit various metallopeptidases such as NEP, which catalyzes the breakdown of vasodilators and antiproliferative peptides (NP, kinins), ACE and endothelin 1. Several drugs of this group are known: omapatrilat fasidotril, mixampril, sampatrilat, CGS30440, MDL100, 240, Z13752A, among others. (Sagnella, 2002)

The most representative drug of this group is omapatrilat, a dual inhibitor of ACE and NEP. This inhibition results in an increase in vasodilator mediators (PN, adrenomedullin, kinins, prostacyclin-PGI 2, NO) and a reduction of vasoconstrictors (Ang II, sympathetic tone). Omapatrilat causes a reduction in systolic and diastolic BP higher than other antihypertensives (amlodipine, lisinopril), regardless of age, sex and race of the patient. It is well absorbed orally and reaches peak plasma concentrations of 0.5-2 h. It presents a half life

of 14-19 h, allowing the administration of the drugs once a day. It is biotransformed into several inactive metabolites which are eliminated by the kidneys.

The OCTAVE study (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) conducted in 25 267 hypertensive patients, confirmed the appearance of pictures of angioedema in omapatrilat treated patients, showing that the incidence of angioedema was 3 times higher than in patients treated with an ACE inhibitor, while in the OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) performed in 5770 patients with HF, functional class II-IV, ejection fraction ≤ 30% was 0.8% in patients treated with omapatrilat and 0.5% in those treated with enalapril. This dangerous side effect has stopped marketing the product. The simultaneous inhibition of ACE and NEP, both involved in the degradation of bradykinin, could lead to an accumulation of bradykinin and be responsible, at least in part, of the angioneurotic edema. (Sagnella, 2002)

5. Antagonists of endothelin receptors

Endothelins are a group of peptides discovered in 1988, produced by endothelial cells (ET-1, ET-2 and ET-3). They are one of the most potent vasoconstrictors known. The actions of endothelin ET-1 in humans are mediated through ETA receptors (present in smooth muscle cells of the vessels) and ETB (present on endothelial cells). Endothelins have been implicated in various cardiovascular diseases such as hypertension and HF. (Dhaun et al., 2008)

ET-1 acts on two receptor subtypes: the ETA, located in vascular smooth muscle cells, the myocardium, the fibroblasts, the kidney and the platelets, and the ETB, located on endothelial and vascular smooth muscle cells and in the macrophages. The ETA receptor stimulation produces vasoconstriction, fluid retention, proliferative effects, cardiac hypertrophy and releases norepinephrine and Ang II, and the ETB produces vasodilatation by releasing NO and eicosanoidsfrom endothelial cells and vasoconstriction by stimulating receptors on vascular smooth muscle cells. The ET-1, via ETA receptor stimulation also stimulates the release of cytokines and growth factors (vascular endothelial, of fibroblastic growth, platelet TGF-β) and facilitates platelet aggregation.

Several are the antagonists of endothelin receptors known so far as: ETA (darusentan sitasentan, LU135252); ETB (BQ788) and ETA/ETB (bosentan enrasertan, tezosentan). All these drugs produce beneficial hemodynamic effects in short term treatment, which raised great expectations in its use in hypertension treatment. There are numerous preclinical studies carried out in animals with antagonists of ETA receptors and ETA/ETB mixed antagonists, showing a decrease in BP in them.

Bosentan, a ETA/ETB mixed antagonist, has been used in clinical trials for the treatment of hypertension and HF, being effective in both situations and with tolerance generally acceptable in short term studies. Treatment with bosentan for 4 weeks reduced BP in hypertension as much as 20 mg of enalapril. It is important to notice that, this reduction was achieved without the activation of the sympathetic nervous system or RAAS.

In another study with darusentan, an ETA selective antagonist; in reducing systolic and diastolic BP compared with placebo was also effective. Its most common side effects are headache, facial redness and edema in lower extremities, and liver chemistry changes. Due

to the limits of these studies, the role of these drugs is yet to be determined, because they have found significant adverse effects such as teratogenicity, hypertransaminemia and so its use has been limited by the FDA. (Krum et al., 1998)

The future of these drugs is uncertain. The results of human trials with these drugs have not reached the results from animal models. To date, these compounds have only been approved for use in patients with pulmonary arterial hypertension. Although they may reduce BP, there are antihypertensive drugs, safer and better tolerated available. However, the biological understanding of endothelin is rapidly evolving and its role in endothelial dysfunction of cardiovascular diseases is still a promising via in the pathogenesis and treatment of hypertension.

6. Ouabain antagonists

The sodium pump is the major cellular carrier system that controls sodium homeostasis and membrane potential, both key factors in the regulation of vascular tone and BP. Several experimental evidences suggest that increased endogenous levels of inhibitor prototype of the sodium pump, endogenous ouabain, may participate at least in part, in the pathogenesis of hypertension. (Hamlyn & Manunta., 2011) Chronic administration of ouabain to rats produces hypertension and increases, probably as a compensatory mechanism, negative endothelial modulation of vasoconstrictor responses produced by the endogenous vasodilator NO. (Manunta et al., 2009)

Endogenous ouabain is a fast action circulating hormone, which is present in several species. It is stored and secreted by the hypothalamus, the pituitary and the adrenal glands. In the latter it synthesized in the fasciculata cells zona from progesterone and pregnenolone through various isomers of 3β-hydroxyesters dehydrogenases. The synthesis in the hypothalamus and the pituitary gland has not been clarified yet. It has a half life of 5 to 8 minutes and is eliminated by the liver and kidney. It is humerally secreted by the exercise and the hypoxia through phenylephrine and Ang II by AT2 receptor by means of systems not yet well known. (Manunta et al., 2009)

On the other hand, for more than 200 years the ouabain (G-strophanthin) have been used to treat HF, an arrow poison of the African Ouabaio tree and of Strophanthus gratus plants. (Schoner.,2002). By radioimmunoassay techniques, it has proved that its half-life is of 21 hours in human and renal clearance. It has been found to be the predominant route of excretion and biliary excretion has been estimated at only 2-8%. (Selden, Smith & Findley, 1972)

The blocking action of cardiotonic steroids in sodium pump holds α receptors and has been shown in almost all animals and all types of cells. The sodium pump, the sodium (Na)-potassium (K) adenosine triphosphatase, Na+/K+-ATPase, has four isomers α receptors, α-1, α-2, α-3 and α-4. The α-1 is specific for Na+ and is present throughout the cell membrane. α-2 and α-3 receptors are less related to Na+ and are associated with the activity of the exchanger protein $Na+/Ca^{2}+$, NCX 1.3. Each cell type has a different proportion of these receptors, α-3 receptors are more numerous in nerve, myocardial and arterial smooth muscle cells, α-2 receptors are more abundant in striated muscle and α-1 receptors are more abundant in the kidney. The ouabain receptor acts mainly on α-3 and also in the α-2 recptors but with less affinity. Sperm has only the fourth receivers, the α-4 receptors. (Blaustein et al., 2009; Scheiner-Bobis & Schoner., 2008)

A new antihypertensive agent, rostafuroxin (PST2238) a digitalis derivative, has been developed due to the ability to correct abnormalities of the Na-K pump. It is endowed with high potency and efficacy in reducing BP and preventing organ hypertrophy in animal models. (Ferrari et al., 2006) At the molecular level in the kidney, rostafuroxin normalizes the increased activity of the Na-K pump induced by adducin mutants pump and endogenous ouabain. In the vasculature, it normalizes the increasement of myogenic tone caused by endogenous ouabain.

A very high safety factor is the lack of interaction with other mechanisms involved in the regulation of BP, along with evidence of high tolerability and efficacy in hypertensive patients point to the rostafuroxin as the first example of a new class of antihypertensive drug designed to antagonize endogenous ouabain and adducin. Phase II clinical trial was recently completed, Ouabain and Adducin for Specific Intervention on Sodium in Hypertension Trial (OASIS-HT), in which rostafuroxin was used with encouraging results as 23% had a significant decrease in BP. In the future we will have to wait to compare the results of rostafuroxin with other antihypertensive drugs to be validated as ACE inhibitors and ARBs and its influence on the control of BP. (Staessen et al., 2011)

7. Aminopeptidase A cerebral inhibitors

Aminopeptidases (AP) are proteolytic enzymes ubiquitously distributed, capable of hydrolyzing the aminoterminal amino acids of peptides and polypeptides that have an important role in controlling them centrally, as well as in peripheral tissues and blood. Their activities reflect the functional state of their endogenous substrates.

The terminology is confusing in relation to aminopeptidases, since the same enzyme is usually identified by different names. Aminopeptidase A (EC 3.4.11.7) hydrolyses the terminal of amino acids, mainly glutamic residues, but is also able to recognize the terminal of aspartic, so this enzyme is also known as aminopeptidase glutamate(GluAP).(Bodineau et al., 2008)

Several aminopeptidases (angiotensinase) are involved in the metabolism of the major active peptides of the RAAS. In particular, they are involved in the metabolism of Ang II, Ang III, Ang IV and Ang 2-10. Ang III is derived from the metabolism of Ang II by the action of the GluAP that hydrolyzes the peptide bond with an acid residue, Asp. The AlaAP and/or the ArgAP metabolizes Ang III to Ang IV by hydrolysis of the amino terminal Arg. The Ang I is transformed to Ang 2-10 by the action of the AspAP after the release of amino terminal Asp. The Ang III is a less potent vasoconstrictor than Ang II. It stimulates adrenal secretion of aldosterone, a neural stimulator and has the same affinity for the AT1 and AT2 receptors. Ang IV has little affinity for the AT1 and AT2 receptors and a lot for the AT4 receptor. Ang IV has an important role in regulating local blood flow, including the brain, but also has been assigned a role in cognitive processes, stress, anxiety and depression. Ang 2-10 opposes the vasoconstrictor effect of Ang II.

However, it is also said that this peptide would lead to aortic contraction dose dependent, through the AT1 receptor. Now, in regard to BP control, working with the hypothesis of a coordinated action of different peptides of the system acting together on the AT1, AT2 and AT4 receptors. Wright and colleagues (Wright & Harding, 1992, Wright & Harding, 1994, Wright & Harding, 1997) analysed the role of brain aminopeptidases in hypertension in several studies. They demonstrated that after intracerebroventricular injection of Ang II and

Ang III more sensitivity and a more prolonged increase in BP was observed in genetically hypertensive rats (GHR) than in normotensive Wistar-Kyoto (WKY) and Sprague-Dawley rats. But if previously treated with bestatin (an inhibitor of AlaAP and ArgAP), which prevents the conversion of Ang III to Ang IV, elevation of BP was enhanced and prolonged. These results indicate, therefore, that dysfunction in the central aminopeptidases activity could lead to Ang II and Ang III act longer and therefore, could carry out a progressive and sustained elevation of BP in RGH rats.

Later, Jensen and colleagues showed that in addition to bestatin, a GluAP inhibitor (amastatine), was injected by intracerebroventricular via, which inhibited the formation of Ang III, which is induced BP increase in rats WKYy the GHR so that there should be an effect mediated by the brain RAAS. They also noted that genetically hypertensive rats were more sensitive to the action of inhibitors than the normotensive ones. (Jensen et al., 1989)

RB150 is a prodrug with a specific inhibitory action on aminopeptidase A EC33, when administered intravenously, it inhibits cerebral aminopeptidase A, the Ang III formation and reduces BP over 24 hours in DOCA-salt rats. Thus aminopeptidase A cerebral inhibitors represent a potential antihypertensive treatment. (Bodineau et al., 2008)

In conclusion, although the discovery of ACE inhibitors and ARBs were two important milestones in the treatment of hypertension, the study of other RAAS components that act at both peripheral and central levels offer new therapeutic possibilities. The cerebral Ang III is a potent hypertensive factor. However, Ang 2-10 seems to contribute more to reduce hypertension. The results we have so far indicate that they fundamentally prevent the formation of cerebral Ang III, or perhaps also facilitates the formation of Ang 2-10, a line of research that could develop possible treatments for hypertension.

Therefore, recent studies on central inhibitors of GluAP, responsible for the formation of Ang III, may provide promising results. It is also increasingly clear that to properly understand the brain's control of the BP, studies should consider the bilaterally of the peripheral and central nervous system. The development of agonists and antagonists specific of the ACE-2, may offer an understanding of the pathophysiological role of ACE 2 in the modulation of the BP.

8. Modulators of the endocannabinoid system

The endocannabinoid system (ECS) is a new regulatory system capable of modulating a variety of physiological effects, consisting of endogenous ligands, specific receptors and mechanisms of synthesis and degradation. Endogenous ligands are a new class of lipid regulators among which there are amides and esters of polyunsaturated fatty acid chain. Endocannabinoids are defined as endogenous compounds, produced in different organs and tissues, capable of binding to cannabinoid receptors. The cannabinoids are synthesized "on demand", when they are needed, and released abroad immediately after their production. Its major molecular targets are the cannabinoid receptors (CB) type 1 and type 2 (Brown, 2007). The CB1 receptor is predominantly expressed in the central nervous system, but is also present at much lower, yet functionally relevant levels in various peripheral tissues, including the myocardium, postganglionic autonomic nerve terminals, and vascular endothelial and smooth muscle cells as well as the adipose tissue,liver, and skeletal muscle. The expression of CB2 receptors was thought to be limited to hematopoietic and immune

cells, but they have recently been identified in the brain, the liver, the myocardium, and in the human coronary endothelial and smooth muscle cells. (Pacher et al., 2008)

Increased ECS activity also contributes to the generation of cardiovascular risk factors in obesity/metabolic syndrome and diabetes such as plasma lipid alterations, abdominal obesity, hepatic steatosis, and insulin and leptin resistance. However, the ECS may also be activated as a compensatory mechanism in various forms of hypertension where it counteracts not only the increase in SP, but also the inappropriately increased cardiac contractility through the activation of CB1 receptors. In addition, the activation of CB2 receptors in endothelial and inflammatory cells by endogenous or exogenous ligands was found to limit the endothelial inflammatory response, the chemotaxis, and the adhesion of inflammatory cells to the activated endothelium with the consequent release of various proinflammatory mediators, which are key processes in the initiation and progression of atherosclerosis and reperfusion injury as well as smooth muscle proliferation. (Pacher et al., 2008)

Currently, several types of endogenous cannabinoids have been identified, all of lipid nature and derived from polyunsaturated fatty acids of long chain. Anandamide (N-araquidonoiletanolamina, AEA) and 2-arachidonoylglycerol (2-AG) are the two best known endocannabinoids. AEA may be a partial or full agonist of CB1 receptors with low action over CB2 and 2-AG an agonist both of CB1 and CB2 receptors (Bisogno., 2008, Howlett., 2002).

The possible antihypertensive effect of cannabinoid ligands is based on the lowering of BP seen in the chronic use of cannabis in humans and in response to the acute or chronic administration of tetrahydrocannabinol in experimental animals. (Bisogno., 2008)

Recently there are results that demonstrate its high hypotensive efficiency in hypertensive animals compared with the normotensive ones and evidence that the tonic activation of the ECS in various experimental models of hypertension could be a possible compensatory mechanism. (Batkai et al., 2004, Wheal et al.,2007) This hipotensive tone could be attributed to a decrease in the mediated activity by the CB1 receptor in myocardial contractility rather than vascular resistance. So preventing the degradation of endogenous AEA by pharmacological inhibition of amidohydrolase fatty acid increases myocardial levels of AEA reducing BP and cardiac contractility in hypertensive rats but not in the normotensive ones. Perhaps the amidohydrolase fatty acid could be a therapeutic target in hypertension, where its inhibition would not only reduce BP but also prevent or stop the development of cardiac hypertrophy. (Lépicier et al.,2006)

The adverse side effects of these new drugs, their interaction with other ones, their pharmacokinetics, and their efficacy in the medium and long term, their probable use in other diseases are among the many questions that remain to be clarified in this new but promising group of antihypertensive drugs.

9. Urotensin II receptor antagonists

Human urotensin II (U-II) is a neuropeptide with the most potent vasoconstrictor action known to date. It is even 10 times more potent than endothelin 1. Although known since 1960, it only became a major goal of clinical research recently. It has a wide range of vasoactive properties according to their anatomical location and species studied.

The U-II binds to an urotensin II receptor, Gq protein (UT), originally known as orphan GPR14 receptor. This receptor has been identified in central nervous system cells, the bone marrow, the kidneys, the heart, the vascular smooth muscle and the endothelial cells. (Ames et al., 1999) Using immunohistochemistry techniques, U-II has been found in blood vessels of the the heart, the pancreas, the kidney, the placenta, the thyroid, the adrenal glands and in the umbilical cord. UT stimulation induces the release of NO, prostacyclin, prostaglandin E2 and endothelium derived factors that balance the contractile effect on vascular smooth muscle. Vasoconstriction is mediated by receptors in the vascular smooth muscle, whereas the vasodilatation is mediated by the endothelium. However, in HF and essential hypertension, the U-II loses its vasodilator capacity. So the U-II causes vasoconstriction of endothelium independently and vasodilatation of endothelium dependently.

The complex and contrasting vascular actions of U-II is not only dependent on the condition of the endothelium, but also on the type of vascular bed and species. (Ames et al., 1999, Liu et al.,1999, Matsushita et al.,2001, Maguire et al., 2004, Zhu et al.,2006)

In healthy individuals, the U-II acts as a chronic regulator of vascular tone. In patients with cardiovascular diseases, the balance is lost and elevated plasma levels of U-II in patients with HF, carotid atherosclerosis, kidney failure, diabetes mellitus, liver cirrhosis with portal hypertension and essential hypertension is found.

Endothelial dysfunction causes vasoconstriction or inadequate vasodilatation resulting in a myocardial ischemia and hypertension, associated with an increase in the U-II and UT. In fact, in patients with hypertension U-II is increased 3 or 4 times, and has shown positive correlation between HF and plasma levels of U-II. (Matsushita et al.,2001, Douglas et al.,2002, Richards et al.,2002, Cheung et al.,2004; Suguro et al.,2007)

Today there are several drugs that act on antagonism receptor of U-II: urantide, BIM-23 127, SB-611 812, palosuran. All at different stages of clinical research, so that in the coming years we will have results that allow us to evaluate the effectiveness on BP control and its impact on cardiovascular diseases. (Tsoukas, Kane & Giaid A., 2011)

10. Potassium channel openers

The openers of potassium channels (KCOs) are a class of drugs with an extreme chemical diversity; they include different structural classes such as benzopirans, cyanoguanidines, thioformamides, and pyrimidines. They base their action on the increase of transmembrane K^+ flow, resulting in a hyperpolarization of the cell membrane through the opening of potassium channels and the closing of Ca^{2+} channels, as a result the cell is less excitable and less prone to stimulation. There are two large families of potassium channels described in smooth muscle: channels regulated by voltage and channels regulated by ATP. (Moreau., et al. 2000) Potassium channels, regulated by intracellular ATP are located in the heart and blood vessels and are important modulators of cardiovascular function. The opening of potassium channels produces an increase in K^+ efflux from the cell so that the membrane potential at rest becomes more negative (hyperpolarization) and this leads to inhibition of calcium entry or an indirect antagonism of calcium, causing a drop in intracellular calcium concentration, relaxation of vascular smooth muscle cells and therefore vasodilatation.

(Wang, Long & Zhang., 2004) The primary target for KCOs action is through the regulatory subunit of the KATP channel, known as the sulfonylurea receptor or SUR, an ATP-binding cassette protein. (Moreau., et al. 2000)

These drugs came into use in 1980 in Japan with the commercialization of nicorandil, but now availability is wide and includes: celikalim, levcromakalim, birnakalirn, pinacidil, rilmakah, minoxidil, diazoxide and iptakalim among many others. KCOs like minoxidil, diazoxide, nicorandil, pinacidil, cromakalim and levcromakalim act by enhancing the ATPase activity of SUR1 subunit and the resultant channel opening causes hyperpolarization. (Sandhiya & Dkhar 2009)

Some of these drugs have been developed for clinical use and have several advantages such as its sustained and strong action on lowering blood lipids compared with other antihypertensive drugs.

The disadvantage is its lack of selectivity, thus besides smooth muscle cells, both the pancreas and the heart contain high concentrations of K^+ channels sensitive to ATP, so that the hypotensive effect is accompanied by other side effects such as hyperglycemia and cardiotoxicity, although changes in the chemical structure have produced good results, that are still not good for widespread use such as antihypertensive drugs. (Butera & Soll, 1994)

Diazoxide and minoxidil are currently recommended for the management of hypertensive emergencies and severe resistant hypertension, especially in patients with advanced renal disease. Their routine use as antihypertensive agents is limited because of a reflex increase in heart rate due to the stimulation of the sympathetic nervous system in response to arterial vasodilatation causing flushing, headache and/or sodium and water retention. Therefore, KCOs should be administered in conjunction with a diuretic and b-adrenergic blocker to control reflex increase in heart rate. An increase in plasma renin activity (largely due to activation of the sympathetic nervous system) and aldosterone level may also occur. Hyperglycemic effects of diazoxide and possible hypertrichosis with minoxidil also limit their longterm use, particularly in women. (Jahangir & Terzic 2005)

Recently a new KCOs sensitive to ATP has been developed: the iptakalim, which selectively relaxes small arteries with a more powerful action in hypertensive states. The iptakalim increases NO associated with increased intracellular calcium in cultured aortic endothelial cells. In addition, the iptakalim inhibits the synthesis and release of endothelin 1 associated with reduced RNA messenger of ET 1 and of the ECE. It inhibits the over expression of molecular adhesion in aortic endothelial cells subjected to metabolic disturbance induced by low density lipoprotein, homocysteine, or hyperglycemia, so it can reduce vascular and cardiac remodeling and endothelial dysfunction. (Wang et al., 2007)

Therefore, the protective profile of iptakalim may not only be due to the controlling of BP but may also relate to its effects in the endothelium system. Iptakalim has a selective antihypertensive efficacy with steady and long-lasting characteristics and produces less side and toxicity effects under the effective doses. It has the virtue for hypertension treatment by reversing hypertensive cardiovascular remodeling and protecting the target organs. (Wang, Long & Zhang.,2005)

However, cardioprotective and antiischemic properties of KCOs, beneficial effects on glycation and plasma lipids and bronchial smooth muscle relaxation still makes potassium

channel openers an attractive antihypertensive class in patients with ischemic heart disease, diabetes mellitus and bronchospastic disease.

11. Vascular NAD(P)H oxidase inhibitors

The involvement of oxidative stress in hypertension is well known. There is strong evidence that oxidative stress is increased in essential hypertension, renovascular hypertension, preeclampsia and hypertension induced by cyclosporine.

Hypertensive patients have significantly higher levels of hydrogen peroxide (H_20_2) in plasma than the normotensive ones. Besides the normotensive ones which have a family history of hypertension have an increased production of H_20_2 than those who have no family history of hypertension, suggesting that there may be a genetic component in the high production of H_20_2. (Stocker & Keaney, 2004)

The NAD(P)H oxidase is the largest supplier of superoxide (O_2^-) in blood vessels and its expression and actions are regulated by Ang II through AT1 receptor. It has been shown that NAD(P)H oxidase contributes to the pathogenesis of hypertension. (Matsuno et al., 2005, Gavazzi et al., 2006)

The NAD(P)H oxidase is found in neutrophils and has five subunits: p67phox, p40phox, p22phox, and gp91phox catalytic subunit (also known as "NOX/DUOX family"), with 7 counterparts known to date, with diverse biological functions in different tissues such as: the colon, the blood vessels, the lungs, the heart, the kidneys, the nervous system, the ear, the bones, the testicles, the thyroid and lymphoid tissues. (S Wind et al., 2010)

Though the interaction of subunits in cardiovascular cells and its regulation and function of each NOX/DUOX is still uncertain, it is clear that NOX/DUOX enzymes are very important in normal biological response and contribute to cardiovascular and renal disease, including atherosclerosis and hypertension.

The development of specific inhibitors of these enzymes has attracted attention for its potential therapeutic use in hypertension. Experiments have shown that inhibitors of NAD(P)H decrease the release of O_2^- and increase the synthesis of NO, thus lowering BP. So far, two specific inhibitors: gp91ds-tat and apocynin have been proven to reduce BP in animals in labs. Other inhibitors such as diphenylene iodonium, aminoethyl benzenesulfono fluoride, S17834, PR39 and VAS2870, have proven to be effective in vitro, its effectiveness, pharmacokinetics and specificity is to be determined in vivo. (S Wind et al., 2010)

Many of these drugs not only inhibit the NAD(P)H oxidase but also other enzyme systems and cannot be administered orally, so its clinical use is limited. In addition, reactive oxygen species are so important to the immune and vascular health of human beings as for the disease, so not discriminating against the inhibition of NAD(P)H oxidase derived from reactive oxygen species could produce dangerous side effects.

Other drugs such as ACE inhibitors, ARBs and drugs lowering cholesterol like statins have also shown that they attenuate the activation of NAD(P)H oxidase, so this could be a promising avenue in the search for molecules with specific activities over enzymatic systems involved in cardiovascular diseases.

12. Vaccines

The first attempts to produce a vaccine for hypertension was conducted in the early 50s of the twentieth century and were focused on the RAAS. At that time immunogen renin was employed, demonstrating an antihypertensive action. However, its development was abandoned when observing the appearance of an autoimmune disease characterized by the deposition of antibodies antirenin in the juxtaglomerular apparatus and progressive interstitial inflammatory lesion in the kidney in animal models studied. (Goldblatt, Haas & Lamfrom, 1951, Michel et al., 1987)

Years later in the 60s, interest is focused on vaccines used against Ang I, but these had no antihypertensive effect. (Downham et al., 2003) At present, interest is focused on Ang II as an immunogen agent using a new immunization technology that combines antigens on the surface of a structure of virus like particles (VLP) generating a B cell response against autoantigens. VLPs conjugated to Ang II (CYT006-AngQb vaccine) have been tested in preclinical and clinical trials and have been observed to be well tolerated, immunogenic and with a high proportion of respondent individuals.

In Phase I studies, the tolerability, safety and immunogenicity of the vaccine was assessed after injection of the vaccine in 12 healthy subjects. They noted that the vaccine was well tolerated, safe and rapidly produced levels of specific antibodies to Ang II, which descended over time. (Ambühl et al., 2007) In Phase II B trials, in order to evaluate the effective response dose, the effect of the administration of 100 or 300 micrograms of the vaccine (CYT006-AngQb) or placebo to 72 patients (65 men and seven women with a average age 51.5 years) with moderate hypertension had been analyzed. The administration of the vaccine or placebo was performed at zero, four and twelve weeks. After twelve weeks of follow up, we observed that vaccination with CYT006-AngQb induced a dose dependent response, so that the title of antibodies to Ang II was greater in patients who received doses of 300 micrograms. The BP changes were evaluated at week 14. It was observed that patients who received 300 micrograms of vaccine significantly reduced the daytime systolic BP by 5.6 mmHg and diastolic by 2.8 mmHg compared with placebo recipients. (Tissot et al., 2008)

However, more studies on the beneficial effects of vaccination against hypertension are still needed, its long term effects, its influence on target organ damage and mortality.

13. Renal sympathetic denervation

The role of afferent renal nerves in the pathogenesis of hypertension has been well studied in animal models. Renal denervation in animal models with renal chronic or renovascular failure result in attenuation of the BP. The depressing effect of renal denervation in these models is not caused by changes in renin activity or sodium excretion, but with reduced adrenal sympathetic activity. These findings suggest that afferent renal nerves contribute to the pathogenesis of renovascular hypertension and renal failure, due to the increase of the sympathetic nervous system activity. Moreover, selective afferent renal denervation by dorsal rhizotomy has confirmed that the depressing effect of renal denervation in these models is due to the interruption of renal afferent activity. Similar reductions of muscle sympathetic nerve activity recorded in the peroneal nerve was observed after therapeutic nephrectomy in patients with advanced renal disease, confirming the relationship between afferent sensory fibers of the kidney and central sympathetic activity. (Fisher & Paton, 2011)

In a study coordinated by researchers at Monash University in Melbourne (Australia) and published in The Lancet, the use of renal denervation, a technique based on the use of a catheter to clear the neural activity of the kidneys, could be useful in the approach of people with resistant hypertension. The Symplicity HTN-2 trial was a multicenter, prospective, randomized, and controlled study about safety and efficacy of renal sympathetic denervation in patients with uncontrolled hypertension.

The device (Simplicity Catheter; Ardian Inc, Palo alto, California) is a catheter that is inserted through the end of the renal artery and then the tip is removed slowly, rotating and emitting radio frequency motions to suppress nerve activity. (Fig.1)

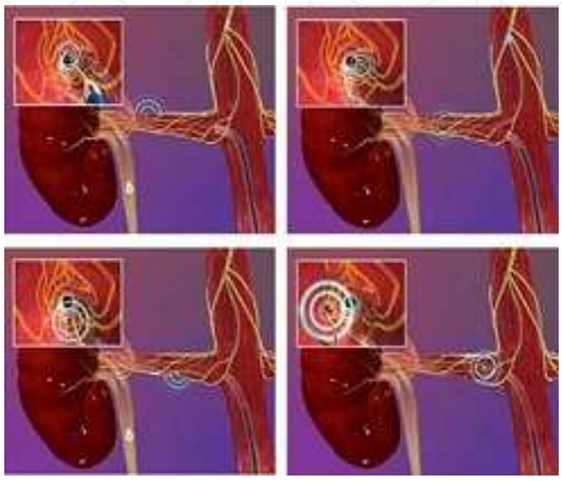

Fig. 1. Percutaneous renal denervation procedure. Graphic of catheter tip in distal renal artery. Reproduced from Krum, H. et al. (2009)

The study included a total of 106 patients from 24 hospitals in Australia and Europe. Both the treatment and control groups at baseline had high levels of BP (178/97 mmHg and 178/98 mmHg respectively), despite receiving intensive antihypertensive treatment, with an average of five drugs. After six months of beginning the trial, the average number of BP of the group that received renal denervation treatment was reduced to 146/85 mmHg, while the control group had a mean of 179/98 mmHg. (Krum et al., 2009)

Witkowski and colleagues evaluated the effects of renal denervation on BP and sleep apnea severity in patients with resistant hypertension and sleep apnea. They studied 10 patients with resistant hypertension and sleep apnea, who underwent renal denervation and completed 3 month and 6 month follow-up evaluations, including polysomnography and selected blood chemistries, and BP measurements. Antihypertensive regimens were not changed during the 6 months of follow up. Three and 6 months after the denervation, decreases systolic and diastolic BPs were observed. Significant decreases were also observed in plasma glucose concentration 2 hours after glucose administration and in hemoglobin A1C level at 6 months, as well as a decrease in apnea-hypopnea index at 6 months after renal denervation. (Witkowski et al., 2011)

In another study, a total of 11 patients received renal denervation treatment. Patients were followed up for 1 month after treatment. No periprocedural complications or adverse events during follow up were noted. A significant reduction of BP was seen at 1 month follow up.

Also, They noted a significant decrease in aldosterone level,while there was no decrease in plasma renin activity and in the renal function. (Voskuil et al.,2011)

Although the treatment is minimally invasive and presented no apparent complications, it is reserved only for patients with resistant hypertension unresponsive to adequate medical treatment. However randomized studies should be conducted with a larger population and a longer follow up term.

14. Baroreflex activation

The influence of the baroreflex in the control of the BP has been known for centuries. As long ago as 1799, Parry described for the first time in humans that carotid compression not only produced bradycardia but also hypotension. (Doumas, Guo & Papademetriou., 2009) When there is elevation in BP the baroreceptors are activated to decrease sympathetic outflow to the heart, kidneys, and peripheral arteries as well as it increases the parasympathetic tone in the heart. The result is a decrease in peripheral vascular resistance, heart rate and BP. The decrease in renal sympathetic tone reduces RAAS activity with resulting reduction of salt and water retention by the kidney and a decrease in the Ang II. The decrease in vasopressin arginine secretion observed during the increase in baroreceptor activity helps reduce systemic vasoconstriction and renal retention of water. That is why the regulatory role of arterial baroreceptors in the fluctuations of BP short term and sustained elevations in BP are well established. (Guyton et al., 1972)

On the other hand, there is accumulating evidence suggesting that sympathetic nerve activity plays an important role in the pathogenesis of essential hypertension. The findings indicate that sympathetic arousal is especially pronounced in patients who are difficult to control BP as in isolated systolic hypertension, hypertension associated with obesity and obstructive sleep apnea and in those with a non-dipper of BP pattern.

Early studies on the role of the baroreflex in the control of BP, were held in 1950 in dogs to which electrical stimulation of the carotid sinus was applied, showing significant decrease in BP in normotensive and hypertensive animals. (Morrissey, Brookes & Cooke., 1953) These data suggest that the baroreflex is important in chronic hypertension and renal sympathetic inhibition with an increase in natriuresis what could be the mechanism by which the baroreflex is involved in controlling long term BP.

After overcoming years of many technical difficulties, Tuckman implanted stimulators in both carotid sinuses allowing the regulation of stimulus achieving a BP reduction without adverse effects for a period of 2 to 18 months. (Tuckman et al., 1972) Other researchers conducted studies with similar results. (Parsonnet et al., 1969, Rothfeld et al., 1969, Brest, Wiener & Bachrach., 1972) Currently several studies are underway with a Rheos device that produces chronic electrical stimulation of the carotid sinuses (CVRx, MN, USA): European and U.S. study Feasibility and Rheos Pivotal trial. (Fig.2)

Rheos system includes a small pulse generator that is implanted under the collarbone, two thin wires that are implanted in the left and right carotid arteries and are connected to the pulse generator and Rheos programmer system: an external device used by physicians for non-invasive control of the energy delivered by the generator to the overhead wires. In the Device Based Therapy of Hypertension study (Debut-HT), 16 patients completed 2 years of

follow up. Both systolic and diastolic BP decreased significantly with 35 ± 8 mmHg and 24 ± 6 mmHg, respectively. In 75% of patients, a decrease in BP of 20 mmHg in systolic BP was shown and 31% achieved BP control. (Scheffers et al., 2008)

In the European and North American study, Rheos system was applied to 16 patients with resistant hypertension which demonstrated a statistically significant decrease in BP in 3 months, along with reduction of left ventricular mass index (-24.1 ± 18.7 g/m^2), of the thickness of the septum (- 1.3 ± 1.8 mm), and of the thickness of the left ventricular posterior wall (-1.4 ± 1.1 mm). These results are also accompanied by reduction in the number of antihypertensive drugs used per patient. (de Leeuw et al., 2008) Another study of 12 patients with Rheos system in patients with resistant hypertension showed no deterioration of renal function after 1 year follow up. (Scheffers, Kroon & de Leeuw., 2008) In another 12 patients with resistant hypertension studied by Heusser, showed that electrical stimulation of the baroreceptors decreased systolic BP in 32 ± 10 mmHg, and this one correlated with a reduction in the muscle sympathetic nerve activity, the heart rate and the concentration of plasma renin. (Heusser et al., 2010)

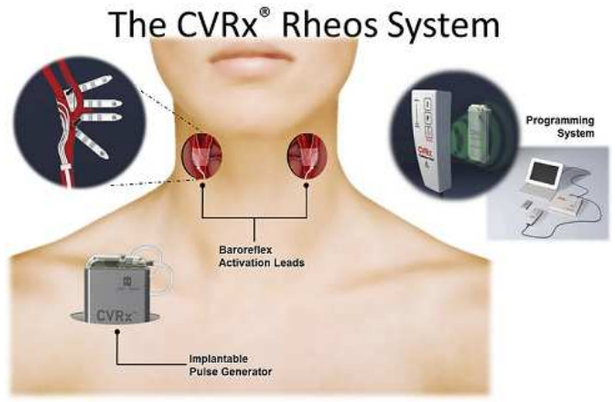

Fig. 2. Rheos System. From CVRx, Rheos, Baroreflex Hypertension Therapy are trademarks of CVRx, Inc. © CVRx, Inc. 2009

At the present time the company CVRx, Inc., the proprietress of this system has announced the introduction of a second generation with an implantable device: The Barostim neo™, with the characteristic to have a smaller generator and a 1 mm unilateral electrode, which should be utilized in resistant hypertension and the HF. (Hasenfuss, 2011)

Without misgivings another investigating step to explain details of efficacy to brief, middle and long term of these devices, their possible interactions with other drugs or surgical procedures, their medical indications, etc., what will permit in the future its use on a wider scale in the resistant hypertension.

15. Crosslink breakers of the end products of advanced glycation

The abnormal collagen cross links due to the formation of the end products of advanced glycation (AGEs) contribute to increase cardiovascular stiffness, which is a predictor of adverse cardiovascular events in old age, hypertension and diabetes. (Vlassara & Palace, 2002, Susic et al., 2004)

The first switch of the cross links of AGEs was phenacylthiazolium bromide (PTB), discovered in 1996, which reacts with cross links of AGEs derived from proteins. The PTB is rapidly degraded, so for the search of a more stable one, alagebrium (4.5 dimethylthiazolium or ALT-711) was discovered. (Dhar, Desai & Wu., 2010) Alagebrium breaks cross links of the end products of advanced glycation. In experimental animal models of advanced age, hypertensive or diabetic, the alagebrium reduced aortic stiffness and systolic BP, decreased the speed of pulse wave, improved diastolic ventricular compliance and cardiac output, improved diabetic nephrosclerosis and reduced urinary albumin excretion. Alagebrium also reduced oxidative stress in experimental elder animals by increasing the activity of glutathione peroxidase and superoxide dismutase. (Dhar, Desai & Wu., 2010) In elderly patients, alagebrium improved arterial compliance, reduced systolic BP and was well tolerated.

Today there are numerous studies underway in elderly patients with isolated systolic hypertension, HF and nephropathy; these results will clarify the likely benefit in the aging and cardiovascular diseases.

16. Rho kinase inhibitors

The intracellular signalling pathway of RhoA/Rho kinase (ROCK) is a mechanism discovered in the mid 90's of the twentieth century by japanese researchers, with a significant participation in the pathological remodeling of cardiovascular diseases. Two isoforms have been identified: the Rock 1 and ROCK 2. (Liao, Seto & Noma., 2007)

The vascular smooth muscle contraction is controlled by the concentration of free cytosolic Ca^{2+} and Ca^{2+} sensitivity of contractile proteins. The sensitization of Ca^{2+} in contractile proteins is determined by means of the RhoA/Rho kinase, which regulates the degree of phosphorylation of myosin light chains (MLC) by the phosphatase phosphorylation of the CLM, keeping the force of generation.

The contraction and relaxation of blood vessels is significantly regulated through phosphorylation and dephosphorylation reactions of the CLM in the regulatory subunit of protein phosphatase 1 target of myosin (myosin phosphatase target protein 1 or MYPT-1). It has been shown that the small GTPase Rho and its effector Rho A kinase modulate the phosphorylation of MYPT-1, so that when intracellular signalling pathway RhoA/Rho kinase is activated MYPT-1 increases. (Liao, Seto & Noma., 2007)

The route of the RhoA/Rho kinase is involved in pathological cardiovascular remodelling and in the regulation of BP and it is activated by agonists of receptors coupled to G membrane protein, such as Ang II, endothelin or noradrenaline, and produces contraction of the smooth muscle cells and hypertension. Rho kinase activation by Ang II is also involved in the oxidative stress and increased production of proinflammatory and profibrotic mediators. ROCK thus promotes oxidative stress and remodeling. (Liao, Seto & Noma., 2007)

Furthermore, RhoA-ROCK pathway is involved in cellular processes involved in the pathogenesis of various cardiovascular and renal diseases, as it participates in the effects of vasoactive and promoting of molecules of cardiovascular and renal remodeling, such as Ang II, 5 hydroxytryptamine, thrombin, platelet derived growth factor, endothelin, norepinephrine, thromboxane A_2 and U II. The activation of ROCK, a target of Rho A also produces a chain of cellular events such as the regulation of endothelial NO synthase

expression by decreasing its gene activation of NAD(P)H oxidase with increased oxidative stress. (Liao, Seto & Noma., 2007) There is sustained evidence that Rho kinase pathway is substantially involved in the pathogenesis of vasospasm, atherosclerosis, hypertension, pulmonary hypertension, stroke and HF and increased central sympathetic nerve activity. (Rikitake & Liao JK., 2005)

The Rho kinase inhibitors (Y-27632, fasudil, hydroxyfasudil, KI-2309) induce relaxation of vascular smooth muscle, decrease in BP and inhibition of cardiovascular remodelling and endothelial dysfunction in hypertensive experimental animals. (Rikitake & Liao JK., 2005)

In hypertensive patients they improve endothelial dysfunction, normalize superoxide production, reduce peripheral vascular resistance and inhibit the development of cerebral and coronary vasospasm. (Masumoto et al., 2001) The first Rho kinase inhibitor approved for clinical use was the fasudil in 1995 in Japan and China, which has been used in cerebral vasospasm resulting from subarachnoid haemorrhage surgery. Several adverse effects such as intracranial bleeding, impaired liver function and hypotension have been reported. (Rikitake & Liao JK., 2005)

As more understanding of the physiological role of each ROCK isoform in the cardiovascular system is needed as well as the development of specific inhibitors of these to solve the specificity and safety of ROCK inhibitors.

17. Antihypertensive drugs with combined mechanisms of action

17.1 Dual inhibitors of neutral endopeptidase and angiotensin II receptors blockers

The Lancet in 2010 published the results of a study by Luis Ruilope and colleagues of LCZ696 a new drug (Novartis), which combines in a single molecule the double blocking action of Ang II and inhibits neprilysin (NEP 24.11) a metallopeptidase membrane that produces degradation of atrial natriuretic peptide, so it would provide the cardiovascular benefits of inhibiting RAAS without causing angioedema. (Ruilope et al., 2010)

This is a double blind multicenter study comparing the effects of LCZ696 with valsartan and another blocker of neprilysin called AHU377. It included 1 328 patients with mild to moderate hypertension, from 134 cities in 18 countries (Argentina, Canada, Denmark, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland, Russia, Slovakia, Spain, Switzerland, Taiwan, and USA) who were treated between Oct/12/2007 and July/7/2008. Aged 18-75 years.

The patients were randomized to one of 8 groups of treatment: LCZ696 100 mg, 200 mg LCZ696; LCZ696 400 mg, 80 mg of valsartan, 160 mg of valsartan, 320 mg of valsartan, 200 mg AHU377, and placebo. The primary endpoint was the mean difference in diastolic blood pressure (DBP) compared among LCZ696 doses and valsartan doses (100 mg vs 80 mg, 200 mg vs 160 mg and 400 mg vs 320 mg) over a period of 8 weeks. The results showed that the decrease in DBP with the dual inhibitor is more effective when compared with valsartan, especially at 200 and 400 mg vs 160 LCZ696 and 320 mg of the latter. The DBP reduction with LCZ696 was a dependent dose. As data to highlight there were no significant adverse effects and no patients had angioedema.

Although, there were very promising results there is still much to clarify respecting its usefulness in the medium and long term, not only in the control of hypertension, but on the prevention and control of target organ damage.

17.2 Dual inhibitors of endothelin converting enzyme and neutral endopeptidase

Endothelin produced by endothelin converting enzyme (ECE) is a potent vasoconstrictor and profibrotic agent, while natriuretic peptides are degraded by NEP which have diuretic, vasodilator and antifibrotic properties, so that in a combination same drug of these actions could have a beneficial effect on cardiovascular remodelling, control of BP and cardiovascular mortality. Recently, several drugs have been synthesized: CGS 26303, CGS 34226, SLV88, SLV306 and SLV388, with which promising effects in experimental animals on cardiovascular hemodynamic independently of the BP have been shown. (Dhaun & Webb., 2011) That is why pre-clinical and clinical studies will be the future stage in these novel drugs.

17.3 NO releasing drugs with dual action: NO releasing sartans + NO releasing statins

Both hypertension and hypercholesterolemia are risk factors of cardiovascular diseases. Both produce endothelial dysfunction and promote the development of atherosclerosis. Increased Ang II levels are correlated with endothelial dysfunction and the expression of ACE activity is increased in hypercholesterolemia and atherosclerosis. Moreover, the oxidative stress is involved in many pathophysiological conditions in the cardiovascular system including hypercholesterolemia, hypertension, diabetes and HF.

The Ang II and the activation of AT1 receptors stimulate NAD(P)H oxidase, generating reactive oxygen species in vascular cells and thus endothelial dysfunction. It has been shown that NO is involved in modulating numerous vital functions and its role is known as the regulator of cardiovascular homeostasis, inflammatory response and cell proliferation of vascular smooth muscle.

The beneficial effects of inhibitors of hydroxy methylglutaryl CoA reductase 3 (statins) have been well tested in the treatment of hypercholesterolemia, a condition which is strongly associated with the development of atherosclerosis. In addition, statins significantly reduce cardiovascular mortality in patients with cardiovascular disease risk and which have direct effects on atherosclerotic plaque stability, NO metabolism, inflammation, endothelial function, oxidative stress and thrombosis. (Shepherd et al., 1995)

Moreover ARBs or sartans have demonstrated its safety and efficacy in controlling hypertension, they have reduced endothelial dysfunction and decreased cardiovascular morbility and mortality in diabetic patients, in hypertensive ones with HF and coronary artery disease. (Brenner et al.,2001, Cohn & Tognoni.,2001, Lewis et al.,2001, Dahlof et al.,2002, Pfeffer et al.,2003) Currently, there are drugs being developed that combine the antihypertensive action of ARBs with the releasing of NO in a single molecule, with the aim of improving the safety profile and effectiveness of their native drugs. Hybrids which combine the action of ARBs with a NO releasing statin, (also called statins sartans-NO), antagonize the effects of Ang II in experimental animals with similar power than losartan or captopril. (Nickenig, 2004) The nitric ester derivatives of pravastatin (NCX 6550) and

fluvastatin (NCX 6553) have demonstrated antiinflammatory and antiproliferative action, so it has potential application in diseases with endothelial dysfunction and vascular inflammation. There are additional properties that make NO releasing statins more effective than the native ones. It has been shown that NCX 6550 inhibits platelet aggregation in vitro and reduces mortality in thromboembolism in experimental animals. (Dever et al., 2007)

Thus, the combination of the beneficial effect of ARBs and statins in a single drug may not only be favorable for the prevention of cardiovascular disease but also contribute to adherence of treatment in patients that need this therapeutics for a long period of time.

17.4 Dual antagonist of angiotensin II and endothelin A receptors

Known is the role of Ang II and ET1 in the pathogenesis of essential hypertension. These substances produce vasoconstriction through the activation of its receptors in vascular smooth muscle: the AT1 and ETA, respectively. Ang II promotes the production of endothelin and endothelin in turn increases the synthesis of Ang II.

Moreover, evidence suggests the interrelation between the endocrine and paracrine systems of Ang II and endothelin. Ang II increases the expression of RNA messenger in endothelial cells. Ang II stimulates the release of ET1 by endothelial cells involving AT1 receptors, Ca_2^+ mobilization and activation of kinase C protein. ARBs produce a significant decrease in BP and reduce endothelial dysfunction and cardiovascular mortality in hypertensive, diabetic and HF patients. Thus, the activation of ETA and/or ETB receptors of ET1 causes contraction of vascular smooth muscle cells and increases BP and an antagonist of ETA/ETB receptors like bosetan decreases BP in patients with essential hypertension. Thus the combination in one same drug of properties AT1/ETA receptors antagonists may have a greater effect than either drug alone and with fewer side effects. Today ETA receptor blockers have been modified to acquire AT1 receptor antagonism.

There are several compounds (MS-248 360, BMS-248360, SB-290 670) that in laboratory animals decreased BP, but these investigations are still in very early stages. (Kowal et al., 2004) But this new class of antihypertensive drug which simultaneously antagonizes the AT1 and ETA receptors promise to be a novel approach in the treatment of hypertension and other cardiovascular diseases.

18. Conclusions

The development of research at the dawn of the millennium, in nanotechnology, genetic engineering and biotechnology for the understanding of the multiple pathogenic mechanisms of cardiovascular diseases and its consequences and hypertension within them, have caused a real boom in the appearance of new therapeutic options for hypertension. About some of them (those that are the most in advanced stages of preclinical and clinical research) we have tried to give a small and modest updating.

Others in earlier stages of experimental research as antagonists of vasopressin receptors (RWJ-676070), NO stimulators and stabilizers: L-arginine, tetrahydrobiopterin (BH4), phosphodiesterase inhibitors PDE-5, N-acetylcysteine, donors of NO (NCX-899,

naproxcinod, LA419), stimulators and activators of cyclic monophosphate guanosine (cGMP): BAY 41-2272, BAY 58-2667, BAY 41-8543, BAY 41-2272, HMR-1766, prostacyclin analogue (beraprost, ecraprost) thromboxane antagonists (KT2-962) and molecules with properties of triple inhibition ECA/ECE-1/EPN with CGS35601, yet there is little published data that permit a satisfactory evaluation. (Trapani et al., 2004, Battistini, Daull & Jeng., 2005)

However, what has been so far advanced allows us to have useful drugs with proven scientific evidence on cardiovascular risk reduction and augur a promising future in reducing cardiovascular morbility and mortality.

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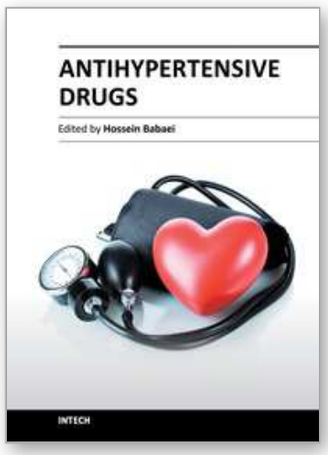

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Hypertension, known as a "silent killer" is widely prevalent and a major risk factor for cardiovascular diseases. It afflicts more than one billion population worldwide and is a leading cause of morbidity and mortality. The authors of the chapters look from different angles to hypertension, sharing their new knowledge and experience in the direction of deep understanding and more clarification of the disease providing an invaluable resource not only for clinicians, but also for all medical sciences students and health providers.

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